(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 July 2004 (01.07.2004)

PCT

(10) International Publication Number
WO 2004/054696 A1

(51) International Patent Classification[7]: B01F 5/00, B01L 9/00

(21) International Application Number: PCT/EP2003/014509

(22) International Filing Date: 15 December 2003 (15.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0229348.8 17 December 2002 (17.12.2002) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: LEGGE, Coulton, Heath [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

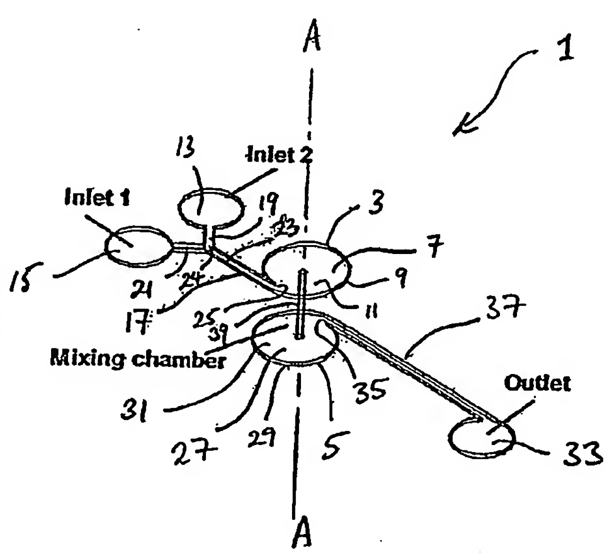
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A MIXING APPARATUS AND METHOD



(57) Abstract: A mixing apparatus (1) for mixing fluids has a first vortex mixer (3) with a first vortex chamber (7), and a second vortex mixer (5) with a second vortex chamber (27) which is in fluid communication with, and located downstream from, the first vortex chamber. The first and second vortex mixers are so constructed and arranged that, in use, the fluids to be mixed are caused to rotatably flow in the first vortex chamber in a first rotating sense (X) and to rotatably flow in the second vortex chamber in a second rotating sense (Y) which is opposite to the first rotating sense. The contra-rotation of the fluids introduces turbulence in the fluids thereby promoting rapid mixing thereof.

WO 2004/054696 A1

A MIXING APPARATUS AND METHOD

Field of the Invention

The present invention relates to the mixing of fluids in vortex mixing apparatus, and is particularly, but not exclusively, concerned with vortex micromixing.

Background of the Invention

The use of microsystems technology, including the use of "on-chip" microfluidics, is now well established in a variety of disciplines, including analytical chemistry, drug discovery, diagnostics, combinatorial synthesis and biotechnology. Such systems may also have important applications where sample volumes may be low, as might be the case in the synthesis or screening of combinatorial libraries, in post-genomic characterisations etc..

In many cases the defining features of microsystems technology, often associated with the term "lab-on-a-chip", is that microfluidic flow rates are relatively high, and channel dimensions small, resulting in faster and cheaper analysis within a smaller footprint. A characteristic effect observed with microfluidic structures results from the inherently low Reynolds Number ($Re<2000$) for such systems, which gives rise to laminar flow. This effect can be most clearly seen when two flowing streams, from different channels, meet to traverse along a single channel, resulting in the streams flowing side-by-side. The net result of this phenomenon is that there is no turbulence, the fluid streamlines do not intermix, and mass transfer between the two streams is limited to the diffusion of molecules across the interfacial boundary layer. Whilst in

principle diffusional mixing across this interface can be fast, with times for mixing ranging from milliseconds to seconds, under high flow rates the distance that the fluid travels along the channel in these times can also be large when compared to the channel dimensions. For example, within a channel of minimum cross-sectional dimension of 50μm and Re=250, the flow velocity of an aqueous solution can be as high as $10ms^{-1}$, and as such little mixing will occur within the chip.

Under the laminar conditions of high flow and small channel dimension, which are characteristic of chip design for many analytical applications, there is a need to enhance the process of fluid mixing in order to increase reaction rates. To this end, a number of active and passive micromixers have been proposed, for instance in 'Microreactors - New Technology for Modern Chemistry', Chapter 3, Ehrfeld *et al*, Wiley-VCH.

Active mixers suffer from fundamental problems which have mitigated against their general usage.

For passive micromixers, the main approach to enhance mixing has been to increase the area of contact between the two flowing streams in order to increase the extent of mass transfer therebetween. However, this technique has resulted in complicated microfabrication procedures and problems of increased backpressure and channel blockage.

A passive micromixer for mixing reactants in a microscale mixing process is disclosed in the paper 'A Rapid Vortex Micromixer for Studying High-Speed Chemical Reactions', Technical Proceedings of Micro Total Analysis Systems, MicroTAS 2001, Monterey, California, USA, S. Bohm *et al* available at www.coventor.com/media/papers. The vortex micromixer

has a vortex chamber with a circumferential side wall and a base wall, a plurality of tangential inlets to the vortex chamber circumferentially arranged about the circumferential side wall, and an axial outlet from the vortex chamber located in the base wall. The liquids to be mixed enter into the vortex micromixer through different inlets.

The use of vortex mixers is also previously known for mixing reactants in macroscale processes. As an example, US patent No. 5,855,776 discloses the use of a number of serially-arranged vortex mixers in a macroscale chemical process. Further vortex mixers for use in a macroscale mixing process are disclosed in EP-A-0153843, GB-A-2253162 and EP-A-0646407.

It is an aim of the present invention to provide means for improved vortex mixing.

<u>Summary of the Invention</u>

According to a first aspect of the present invention there is provided a mixing apparatus for mixing fluids having:-

a first vortex mixer with a first vortex chamber, and

a second vortex mixer with a second vortex chamber which is in fluid communication with, and located downstream from, the first vortex chamber,

wherein the first and second vortex mixers are so constructed and arranged that, in use, the fluids to be mixed are caused to rotatably flow in the first vortex chamber in a first rotating sense and to rotatably flow in the second vortex chamber in a second rotating sense which is opposite to the first rotating sense.

Preferably, each vortex chamber has a chamber axis, a circumferential wall formed about the chamber axis and a port formed in the circumferential wall, the ports of the first and second vortex chambers respectively being inlet and outlet ports, and the mixing apparatus has an inlet conduit which extends to the inlet port in an inlet direction which faces in the first rotating sense and an outlet conduit which extends away from the outlet port in an outlet direction which faces in the second rotating sense. Thus, the inlet conduit is directed to cause the fluids introduced by it into the first vortex chamber to rotatably flow in the first rotating sense, while the outlet conduit is directed so as to be able to receive the fluids when rotatably flowing in the second vortex chamber in the second rotating sense.

Typically, the inlet and outlet conduits have a terminal section at the respective port, the terminal sections having a longitudinal axis which is angled away from the respective chamber axis. Expressed another way, each longitudinal axis is not aligned with (does not intersect with) the respective chamber axis. As an example, the terminal sections of the inlet and outlet conduits may be arranged at an inclined angle to the respective circumferential wall, for instance tangentially.

Preferably, the inlet and outlet ports are arranged at different circumferential locations on the respective circumferential walls. As an example, the ports may be arranged at diametrically opposed, or substantially diametrically opposed, positions, as in the embodiment hereinafter described.

The inlet and outlet directions may extend in a common direction. However, the inlet and outlet directions may be in different directions, e.g. in opposed directions.

The inlet port and/or outlet port may be the only such port of the respective first and second vortex chamber.

In an embodiment of the invention, such as hereinafter described, the inlet and outlet ports are first inlet and outlet ports, the first vortex chamber has a second outlet port and the second vortex chamber has a second inlet port, the second outlet and inlet ports being connected by a transfer conduit extending therebetween to place the first and second vortex chambers in fluid communication with one another.

Preferably, the second outlet port and/or the second inlet port is oriented axially, as in the embodiment hereinafter described.

In an embodiment, such as hereinafter described, the vortex chambers are spaced apart in a predetermined direction along which the respective chamber axes are aligned. The predetermined direction may be a vertical direction. The first and second vortex mixers may then be upper and lower vortex mixers, respectively, or vice-versa.

In an embodiment, such as hereinafter described, the chamber axes are collinear, or substantially collinear.

In an embodiment of the invention, such as hereinafter described, the transfer conduit has terminal sections at the second inlet and outlet ports, respectively, each terminal section having a longitudinal axis which is collinear, or substantially collinear, with the chamber axis of the adjacent vortex chamber. The transfer conduit may be collinearly arranged, or substantially collinearly arranged, with the chamber axes along its length.

In an embodiment, such as hereinafter described, the first vortex chamber and/or second vortex chamber has an end wall in which the second port is formed. Preferably, the end walls face one another.

The mixing apparatus is particularly, but not exclusively, suited for use in mixing of laminar streams of fluids, especially in micromixing processes (microfluidics). In an embodiment of the invention, such as the one hereinafter to be described, the mixing apparatus is sized for use in a micromixing process. That is to say, the mixing apparatus may be a micromixing apparatus.

When the mixing apparatus is a micromixing apparatus, the apparatus is conveniently comprised in a lab-on-a-chip device. In other words, the apparatus is formed in a unitary body, such as a substrate or chip, for instance by machining, moulding or etching, such as dry etching. The body may be of a plastics material, glass, ceramic, or a semiconductor material, e.g. silicon, although other materials could, of course, be used. The first vortex chamber may be formed as a recess in a first side of the body and the second vortex chamber formed as a recess in a second side of the body, preferably located in opposed relation to the first side. As an example, the first and second sides may be upper and lower sides. The inlet conduit may take the form of a groove in the first side, and the outlet conduit may take the form of a groove in the second side. Alternatively, the outlet conduit may be formed to extend from the second vortex chamber, in the second side, to the first side. This has the advantage of being able to position inlet and outlet structures of the mixing apparatus on the same side of the body. As regards the transfer conduit, this may be a bore in the body.

The body may be covered on the first and second sides by a cover layer to enclose the vortex chambers and, optionally, the inlet and outlet conduits. The cover layer(s) may be formed from a transparent material, e.g. glass or plastic, although this is not strictly necessary if visual (human or machine) inspection of the mixing is not needed. The cover layer or layers may further be provided with openings therein to the inlet and outlet conduits. This enables the inlet and outlet conduits to be respectively connected to external inlet and outlet conduits of the micromixing apparatus, e.g. ducts or hosing, through which the fluids, in use, flow.

The body preferably has a dimension (thickness) from the first side to the second side of less than 1000μm, more preferably no greater than 500μm, even more preferably in the range of 350-450μm.

The mixing apparatus may further comprise a fluid drive system for driving the fluid through the apparatus, for example a pump system located upstream of the first vortex mixer, for instance connected to the external inlet conduit, or a vacuum system located downstream of the second vortex mixer, for instance connected to the external outlet conduit. A pump system may have one or more pump units, e.g. syringe pumps.

The mixing apparatus may be formed by providing a body having a first side and a second side, forming a pilot hole through the body from an entrance on the first side to an entrance on the second side, and enlarging the entrances on the first and second sides to form recesses thereon. Grooves may also be formed on the first and, optionally, second sides which intersect the respective recesses. The recesses correspond to the first and second vortex chambers and the pilot hole connecting the recesses forms the transfer conduit. The grooves then correspond to the inlet and outlet conduits.

Alternatively, the mixing apparatus may be integrally formed from a plastics material, e.g. by machining or by a moulding process, such as injection moulding or micro-moulding.

To reduce back-pressures, and also to reduce the probability of blockage, it is preferable that the minimum cross-sectional dimensions of the inlet, transfer and outlet conduits do not decrease in the downstream direction, e.g. the cross-sections are constant along the channel lengths. Moreover, it is preferable that the minimum cross-sectional dimension of the inlet conduit be no greater than the minimum cross-sectional dimension of the transfer conduit and that the minimum cross-sectional dimension of the transfer conduit in turn be no greater than the minimum cross-sectional dimension of the outlet conduit.

The mixing apparatus may have a pair of inlets in fluid communication with the inlet conduit, the inlets arranged to introduce different fluids in side-by-side relation in the inlet conduit. The inlet conduit preferably has branch sections connected to the inlets. Where the mixing apparatus is a micromixing apparatus, the inlets may be formed in the first side of the body.

The mixing apparatus may further have an outlet in fluid communication with the outlet conduit. The outlet may be formed in the first or second side of the substrate.

In a second aspect of the present invention there is provided a method of mixing a plurality of fluids in which the fluids are rotated together in a first vortex chamber in a first rotating sense and

subsequently rotated in a second vortex chamber in a second rotating sense which is opposite to that of the first rotating sense.

The contra-rotation of the fluids in the first and second vortex chambers results in an improved passive mixing of the fluids. The first rotating sense may be clockwise or counter-clockwise, and the second rotating sense the opposite direction.

Conveniently, the contra-rotating steps are successive steps.

The method may be implemented on the mixing apparatus of the invention.

Preferably, the fluids are introduced into the first vortex chamber concurrently, more preferably from a common inlet. The fluids may be introduced concurrently as parallel flow streams, i.e. in side-by-side relation.

Preferably, the first and second vortex chambers are formed in a lab-on-a-chip device, especially if the mixing method is a microfluidic mixing method.

The method should be carried out a flow rate which is sufficient to cause the fluids to be mixed, e.g. to create turbulent flow in the vortex chambers. As an example, the fluids may be caused to flow into the first vortex chamber at a flow rate of greater than 50µl min^{-1}, but no greater than 3ml min^{-1}, preferably in the range of 100µl min^{-1} to 400µl min^{-1}, more preferably in the range 200-400µl min^{-1}, even more preferably in the range of 200-300µl min^{-1}.

The mixing method is preferably a passive mixing method.

The circumferential wall(s) may have a height in the range of 25-100μm, preferably in the range of 40-60μm.

The inlet and/or outlet conduit may have a width or inner diametral dimension in the range of 30-600μm, preferably in the range of 40-60μm, more preferably 50μm or substantially 50μm. Where the inlet and/or outlet conduit has a rectilinear form (i.e. a width dimension), the depth of the inlet and/or outlet conduit may be in the range of 30-300μm, preferably in the range of 40-60μm, more preferably 50μm or substantially 50μm. Preferably, the inlet and/or outlet conduit have a width-to-depth (aspect) ratio in the range of 3:1 to 1:1, or substantially 3:1 to 1:1. The width and depth may be constant, or substantially constant, along the length of the inlet/outlet conduit.

The inlet port and/or outlet port may be formed in the circumferential wall of the associated vortex chamber so as to form a gap in the circumferential wall across the full height thereof. In this case, the height of the circumferential wall and the depth of the inlet conduit are the same, or substantially the same.

The transfer conduit preferably has a width or inner diametral dimension corresponding to, or substantially corresponding to, the width/inner diametral dimension of the inlet conduit and/or outlet conduit. The width/inner diametral dimension of the transfer passage may be constant along its length.

The vortex chamber(s) may have a maximum inner diametral dimension in the range of 100-3000μm, preferably in the range of 200-600μm, more preferably 250-550μm.

The mixing apparatus may have a total dead volume in the range of 100-150nl, preferably in the range of 120-130nl, more preferably 125nl or substantially 125nl.

Preferably, the ratio of the maximum inner diametral dimension of the vortex chamber(s) to the width/inner diametral dimension of the associated inlet conduit and/or outlet conduit is in the range of 5-6:1

According to a third aspect of the present invention there is provided a mixing apparatus for mixing fluids having:-

a first vortex mixer with a first vortex chamber having a chamber axis, and

a second vortex mixer with a second vortex chamber which has a chamber axis and which is in fluid communication with, and located downstream from, the first vortex chamber,

wherein the vortex mixers are arranged in the apparatus so that the chamber axes are axially aligned with the first and second vortex chambers overlaying one another.

The apparatus may have a body with first and second opposed sides, for instance upper and lower sides, and the first and second vortex chambers are respectively formed in the first and second sides of the body.

The vortex chambers are generally cylindrical. The circumferential wall of the first vortex chamber, and optionally the second vortex chamber,

preferably circumscribes a spiral profile in the first rotating sense. In other words, the circumferential wall has a decreasing radius of curvature in the first rotating sense. This feature further promotes the rotation of the fluids in the desired rotative sense.

Ordinarily, the fluids to be mixed will be liquids.

The present invention also provides for the features of the different aspects of the invention to be incorporated into one another.

Other preferred features of the invention are incorporated in the non-limiting exemplary embodiments of the invention which will now be described with reference to the accompanying Figures of drawings.

Brief Description of the Figures of Drawings

FIGURE 1 is a schematic perspective view of a mixing apparatus of the present invention having upper and lower vortex mixers, each having a vortex chamber.

FIGURE 2 corresponds to FIGURE 1 other than showing the mixing apparatus embodied in a substrate of a lab-on-a-chip device.

FIGURE 3A is an enlarged fragmentary cross-sectional view of the vortex chamber of the upper vortex mixer.

FIGURE 3B is an enlarged plan view of the vortex chamber of the upper vortex mixer.

FIGURE 4 is a fragmentary side view, partly in cross-section, of the lab-on-a-chip device showing the substrate overlain with cover layers and fluid connections to the upper and lower vortex mixers.

Detailed Description of the Exemplary Embodiments of the Invention

The FIGURES of drawings show a passive mixing apparatus 1 for mixing liquids having an upper vortex mixer 3 and a lower vortex mixer 5.

The upper vortex mixer 3 has a generally cylindrical vortex chamber 7 arranged about an axis A-A, the chamber 7 having a circumferential wall 9 and a transverse end wall 11. The upper vortex mixer 3 further has an inlet channel structure having a pair of inlets 13, 15, in the form of cylindrical wells or recesses, and an inlet channel 17 of U-shaped cross-section which places the inlets 13, 15 and vortex chamber 7 in fluid communication with one another. More particularly, the inlet channel 17 has a pair of branch sections 19, 21, each intersecting with a different inlet 13, 15, and a terminal section 23 which extends from a junction 24 of the branch sections 19, 21 to an inlet port 25 formed in the circumferential wall 9 of the vortex chamber 7. The inlet port 25 is of the same cross-section as the inlet channel 17.

As will be seen, the longitudinal axis of the terminal section 23 of the inlet channel 17 is oriented at an inclined angle to the circumferential wall 9 of the vortex chamber 7, in this instance tangentially arranged. This results in the liquids inputted into the vortex chamber 7 being caused to rotate in the vortex chamber 7 in an anti-clockwise direction, as indicated by the arrow marked X in FIGURE 2.

The lower vortex mixer 5 is of similar construction to the upper vortex mixer 3. Thus, it has a generally cylindrical vortex chamber 27, which is arranged about the axis A-A, and has a circumferential wall 29, a transverse end wall 31 which faces the end wall 11 of the upper vortex mixer 3, and an outlet channel structure having an outlet 33, in the form of a cylindrical well or recess, and an outlet channel 37 of U-shaped cross-section which extends from a U-shaped outlet port 35 in the circumferential wall 29 to the outlet 33. The longitudinal axis of the outlet channel 37 is oriented at an inclined angle to the circumferential wall 29 of the vortex chamber 27, again tangentially in this instance. Liquids rotate in the vortex chamber 27 in a clockwise direction, as indicated by the arrow marked Y in FIGURE 2, and are passively extracted through the outlet channel 37.

The vortex chambers 7, 27 of the upper and lower vortex mixers 3, 5 are fluidly connected by a cylindrical transfer conduit 39 which extends axially from an outlet port 41 in the end wall 11 of the upper vortex mixer 3 to an inlet port 43 in the end wall 31 of the lower vortex mixer 5. In this way, liquids inputted into the vortex chamber 7 of the upper vortex mixer 3 are transferred to the vortex chamber 27 of the lower vortex mixer 5.

Referring to FIGURE 3B, it will be seen that the circumferential wall 9 of the vortex chamber 7 of the upper vortex mixer 3 circumscribes a spiral path in which the radius of curvature R of the wall 9 decreases monotonically with angular extent from the inlet port 25, i.e. in the anti-clockwise direction X. Although not shown, the circumferential wall 29 of the vortex chamber 27 of the lower vortex mixer 5 also follows a spiral path, with the radius of curvature decreasing with angular extent from the outlet port 35, i.e. also in the anti-clockwise direction X. This geometry assists in causing the fluids to flow in the contra-rotating senses X, Y.

It will be observed that the inlet and outlet channel structures extend away from the associated vortex chambers 7, 27 in opposed directions. Moreover, the inlet port 25 of the upper vortex mixer 3 and the outlet port 35 of the lower vortex mixer 5 are located at generally diametrically opposed positions on the respective vortex chamber 7, 27. Nonetheless, the inlet and outlet channel structures could extend away in non-opposed directions, i.e. in the same direction.

To reduce backpressures in the mixing apparatus 1, and to reduce the probability of blockage, the cross-sections of the inlet, transfer and outlet channels 17, 39, 37 are constant along the lengths thereof, and the minimum cross-sectional dimension of the inlet channel 17 is no greater than the minimum cross-sectional dimension of the transfer channel 39 which in turn is no greater that the minimum cross-sectional dimension of the outlet channel 37. In other words, the minimum channel dimension in the mixing apparatus 1 is determined by the minimum inlet channel dimension.

To this end, the width and depth of the inlet and outlet channels 17, 37 are approximately the same, and the diameter of the transfer conduit 39 is approximately the same as the widths of the inlet and outlet channels 17, 37. Moreover, the depth of the vortex chambers 7, 17, and optionally the inlets 13, 15 and the outlet 33, are the same as the depths of the inlet and outlet channels 17, 37.

In use, the liquids to be mixed are delivered to a different one of the inlets 13, 15, e.g. through pumping or by vacuum pressure, whereupon the liquids form flow streams in the branch sections 19, 21 of the inlet channel 17. The respective flow streams converge at the junction 24 of

the branch sections 19, 21 and then flow in tandem (i.e. in side-by-side relation) as laminar flow streams along the terminal section 17. By introducing the liquids into the mixing apparatus 1 at sufficient flow rates, when the two flow streams enter the vortex chamber 7 of the upper vortex mixer 3 they circulate in the anti-clockwise sense X until they are fed into the vortex chamber 27 of the lower vortex mixer 5 via the transfer conduit 39. In other words, a vortex is driven. Once in the vortex chamber 27 of the lower vortex mixer 5, the liquids flow in the clockwise sense Y and then continue to the outlet 33 via the outlet channel 37. The creation of vortex flows in the upper and lower mixers 3, 5 with contra-rotating senses X, Y imparts turbulence into the flow streams thereby promoting passive mixing of the liquids by enabling convection to contribute to mass transfer. In this way, a mixed liquid is received in the outlet 33. In this regard, having the inlet and outlet channel structures extend away from the associated vortex chambers 7, 27 in opposed directions assists in driving the vortex in the mixing apparatus 1 and creating turbulence.

Referring to FIGURE 2, the mixing apparatus 1 may be embodied in a so-called lab-on-a-chip device (LOAC) 51. The LOAC 51 has a substrate 53 in which the mixing apparatus 1 is formed. The substrate 51 has opposed upper and lower sides 55, 57 and the upper vortex mixer 3 is formed in the surface 54 of the upper side 55, with the lower vortex mixer 5 being formed in the surface 56 of the lower side 57. More particularly, the inlets 13, 15, vortex chambers 7, 27 and the outlet 33 are recesses in the respective surfaces, while the inlet and outlet channels 17, 37 are grooves in the respective surfaces. The transfer conduit 39 is formed as a bore in the body of the substrate 53.

The substrate 53 may be formed with the mixing apparatus 1 therein by a number of microfabrication techniques, for instance by

etching, e.g. wet or dry etching, or by moulding, e.g. injection moulding, such as micro-moulding, or by machining.

Turning to FIGURE 4, the LOAC 51 further has upper and lower covers 59, 61 on the upper and lower sides 55, 57 of the substrate 53, respectively, to cover the upper and lower mixers 3, 5. The covers 59, 61 could, of course, be replaced by a single cover which covers both sides. The covers 59, 61 are transparent when visual or machine inspection of the chemical reaction is needed, e.g. photometry. The covers 59, 61 may be of glass or of a plastics material.

The upper cover 59 is provided with two apertures 63 (only one shown) in alignment with the inlets 13, 15. Concomitantly, the lower cover 61 is provided with a single aperture 65 in alignment with the outlet 33. Each such aperture 63, 65 is connected to a duct 67, 69 through which the liquids to be mixed are passed through the mixing apparatus 1, as indicated by the flow arrows in FIGURE 4.

In an alternative embodiment, not shown, the outlet 33 is also positioned on the upper side 55 with the outlet channel 37 being brought back through the substrate 53 from the lower side 57 to the upper side 55 as a second bore to position all fluidic connections on the upper side 55 of the LOAC 51. This latter format presents some advantages when observing the LOAC 51 under a microscope.

There now follows a number of Examples to demonstrate the efficacy of the mixing apparatus 1 in mixing liquids.

Example 1

The substrate 53 of the LOAC 51 was formed from a 380μm silicon wafer (Compart, UK) and the mixing apparatus 1 was incorporated therein by deep dry etching using a STS-ICP (inductively coupled plasma) process. By deep dry etching in a silicon wafer, the mixing apparatus features were formed with perpendicular walls and with a high aspect ratio. To this end, the wafer was first primed with HMDS, which was subsequently heated for 2 hours on a hotplate at 80°C to remove all water. A 15μm thick AZ4562 photoresist (Shipley) was then deposited as a dry etch mask, using a spin speed of 1000rpm. The photoresist was then exposed through a standard photolithographic mask to create a pattern within the mask that would enable the transfer conduit 39 to be deep dry etched through the wafer. Etching conditions were optimised with a coil power of 600W and an etch step duration of 12sec and a passivation step of 9sec, using a SF_6 flow rate of 130sccm and a C_4F_8 flow rate of 85sccm, enabling the etching of the transfer conduit 39 through the wafer in 80mins. Subsequently, the wafer was cleaned and the AZ4562 masking layer re-deposited using through-chip alignment. The wafer was then re-exposed through a second mask set, and was again dry etched in order to create the inlets 13, 15, the channels 17, 23, the vortex chambers 7, 27 and the outlet 33. This latter etching step took less than 15 mins.

To seal the mixing apparatus 1, and enable observation of the flow, upper and lower covers 59, 61 in the form of 0.5mm thick Pyrex® glass plates were bonded to the upper and lower sides 55, 57 to encase the microfluidic inlet channel structure, the vortex

chambers 7, 27 and the outlet channel structure. In this regard, the silicon and glass plates were clamped together and a small amount of UV hardening epoxy glue (EpoTek UVO-114, Epoxy Technology Inc.) diluted in toluene applied to the edge of the wafer. A uniform layer of adhesive spread between the glass and silicon under capillary force. At a dilution of 3 parts of epoxy to 2 parts toluene w/w, local forces/surface tension prevent the epoxy from entering the channels (see Lab Chip, 2, 65-69, 2002, Igata *et al*). For access to the inlets 13, 15 and the outlet 33, the Pyrex® plates were formed with the apertures 63, 65 by drilling 2mm holes in the plates.

Fluidic connections were provided by using epoxy to seal the ducts 67, 69 in the apertures 63, 65. In this Example, the ducts 67, 69 were silicone rubber tubes with an inner diameter of 1.5 mm, and these were sealed against a glass capillary inserted in the respective aperture 63, 65.

Two 10ml syringe pumps (Cole-Parmer Instrument Company, 74900 Series) were used to control the inlet fluid flow, and deliver equivalent amounts of fluid through the inlets 13, 15 at equal flow rates. The LOAC 51 was observed using either an upright or an inverted microscope, both with an attached CCD, which was connected to a computer. Images of flow and turbulent mixing were captured digitally.

Example 2

A LOAC 51 according to Example 1 was fabricated with the upper and lower vortex mixers 3, 5 being etched in the silicon wafer

53 to a depth of approximately 50μm. Furthermore, the inlet and outlet channels 17, 37 were formed with a width of 50μm, while the vortex chambers 7, 27 were formed with a diameter of 300μm. Lastly, the transfer conduit 39 was formed with an inner diameter of approximately 50μm, i.e. the same size as the minimum cross-sectional dimension of the inlet and outlet channels 17, 37. The total dead (internal) volume of the LOAC 51 was 125nl, or substantially 125nl.

Aqueous solutions of the dyes Ponceau 4R (E124) and Carmoisine (E122) were respectively supplied to the inlets 13, 15 at a flow rate of 250μl min^{-1}. The liquids entered the vortex chamber 7 of the upper vortex mixer 3 as side-by-side laminar flow streams, but exited the vortex chamber 27 of the lower vortex mixer 5 as a mixed liquid due to a vortex being driven and the vortices in the chambers 7, 27 having opposite rotative senses.

Example 3

This Example corresponds to Example 2, other than the diameters of the vortex chambers 7, 27 being increased to 500μm. Again, introduction of aqueous solutions of Ponceau 4R (E124) and Carmoisine (E122) to the inlets 13, 15 at a flow rate of 250μl min^{-1} resulted in a vortex being driven in the mixing apparatus with laminar flow streams entering the vortex chamber 7 of the upper mixer 3, but a mixed liquid exiting the vortex chamber 27 of the lower vortex mixer 5 due to the contra-rotation of the flow streams. The degree of mixing, however, was not as great as in Example 2.

Example 4

In this Example the LOAC 51 was formed on a mesoscopic scale (a mesoscale device), as opposed to the microscale of the previous Examples. More particularly, the substrate 53 was formed from Perspex® and the mixing apparatus 1 formed therein by machining. The Perspex® cover layers 59, 61 and substrate 53 were annealed to form a multi-layer sandwich structure. The fluidic connections were as in the previous Examples.

Example 5

The LOAC 51 of Example 4 was formed so that the vortex chambers 7, 27 had a diameter of 2.9mm, and the inlet and outlet channels 17, 37 had a depth of 0.25mm and a width of 0.55mm. The diameter of the transfer conduit 39 was 0.25mm, while the depth of the chambers 7, 29 was 0.25mm. Introduction of aqueous solutions of Ponceau 4R (E124) and Carmoisine (E122) to the inlets 13, 15 at a flow rate of 2.5ml min^{-1} resulted in a vortex being driven with laminar flow streams entering the vortex chamber 7 of the upper mixer 3, but a mixed liquid exiting the vortex chamber 27 of the lower vortex mixer 5 due to the contra-rotation of the flow streams.

Example 6

The results of Examples 2, 3 and 5 with the dyes was confirmed using the respective LOAC 51 to mix a 5mM solution of 1,10-phenanthrolin (dissolved in ethanol and then diluted with RO water) and 5mM ferrous sulphate. The reaction of the solutions resulted in the formation of a red ferrous complex, which was

measured at 633nm in the outlet channel 37 to quantify the rate of mixing.

As demonstrated by the Examples, the passive vortex driven mixing apparatus 1 of the exemplary embodiments enables the rapid mixing of two laminar streams of liquids, especially within a device operating with a low Reynolds number (Re<2000). The enhanced mixing is caused by the turbulence introduced into the laminar flow streams by the mixing apparatus 1, therefore enabling convection to contribute to mass transfer, rather than just boundary layer diffusion.

Under pressure driven flow, the mixing apparatus 1 has the advantage that it requires no external power source other than the fluid drive system, and is fully scalable, operating at both high and low flow rates in microscale and mesoscale devices.

The mixing apparatus 1 is relatively simple to fabricate and, as a consequence of the fact that the smallest dimension is governed by the input channel, the problems of blockage and high backpressures are alleviated. The mixing apparatus 1 also has the advantage of being spatially compact.

The results indicate that a mixing apparatus in accordance with the present invention will enhance mass transfer under a variety of experimental circumstances, but particularly those of any flow rate in mesoscale (millimetre) channels, and high flow rates in microscale channels. The latter conditions of small devices and fast flow rate are currently those most favoured in many aspects of LAOC usage, particularly in the diagnostic and pharmaceutical industries.

It will be appreciated that there are a variety of other fabrication protocols that could be used for making the mixing apparatus of the present invention than described above with reference to the FIGURES of drawings. As an example, the mixing apparatus could be produced by injection moulding from a plastics material, especially for mass production.

It will also be appreciated that the mixing apparatus 1 of the exemplary embodiment can used in an inverted state, i.e. the upper and lower sides 55, 57 of the LOAC 51 are rearranged to be lowermost and uppermost respectively. A vacuum pump could then be used to draw the liquids through the mixing apparatus 1 in this orientation.

It will be understood by the skilled person in the art that the present invention is not limited to the specific exemplary embodiments herein described, but may be varied, modified and adopt other guises within the scope of the appended claims. Moreover, the specific exemplary embodiments may be modified to include features of the claims and the statements in the section 'Summary of the Invention', for instance the dimensions mentioned therein.

Finally, the use of reference numbers from the FIGURES of drawings in the claims is purely for the purposes of illustration, and is therefore not to be taken as having a limiting effect on the scope of the claims.

CLAIMS:

1. A mixing apparatus (1) for mixing fluids having:-

a first vortex mixer (3) with a first vortex chamber (7), and

a second vortex mixer (5) with a second vortex chamber (27) which is in fluid communication with, and located downstream from, the first vortex chamber,

wherein the first and second vortex mixers are so constructed and arranged that, in use, the fluids to be mixed are caused to rotatably flow in the first vortex chamber in a first rotating sense (X) and to rotatably flow in the second vortex chamber in a second rotating sense (Y) which is opposite to the first rotating sense.

2. The apparatus of claim 1 wherein each vortex chamber has a chamber axis (A-A), a circumferential wall (9;29) formed about the chamber axis and a port formed in the circumferential wall, the ports of the first and second vortex chambers respectively being inlet (25) and outlet ports (35), and the mixing apparatus has an inlet conduit (17) which extends to the inlet port in an inlet direction which faces in the first rotating sense and an outlet conduit (37) which extends away from the outlet port in an outlet direction which faces in the second rotating sense.

3. The apparatus of claim 2 wherein the inlet and outlet conduits have a terminal section (23;27) at the respective port, the terminal sections having a longitudinal axis which is angled away from the respective chamber axis.

4. The apparatus of claim 3 wherein the terminal sections of the inlet and outlet conduits are arranged at an inclined angle to the respective circumferential wall.

5. The apparatus of any one of claims 2 to 4 wherein the inlet and outlet ports are arranged at different circumferential locations on the respective circumferential walls.

6. The apparatus of any one of claims 2 to 5 wherein the inlet and outlet directions are in a common direction.

7. The apparatus of any one of claims 2 to 6 wherein the inlet and outlet ports are first inlet and outlet ports, the first vortex chamber has a second outlet port (41) and the second vortex chamber has a second inlet port (43), the second outlet and inlet ports being connected by a transfer conduit (39) extending therebetween to place the first and second vortex chambers in fluid communication with one another.

8. The apparatus of claim 7 wherein the second outlet port and/or the second inlet port is oriented axially.

9. The apparatus of any one of claims 2 to 8 wherein the vortex chambers are spaced apart in a predetermined direction along which the respective chamber axes are aligned.

10. The apparatus of claim 9 wherein the chamber axes are collinear, or substantially collinear.

11. The apparatus of claim 7 or 8, or of claim 9 or 10 when appended to claim 7, wherein the transfer conduit has terminal sections at the second inlet and outlet ports, respectively, each terminal section having a longitudinal axis (A-A) which is collinear, or substantially collinear, with the chamber axis of the adjacent vortex chamber.

12. The apparatus of claims 10 and 11 wherein the transfer conduit is collinearly arranged, or substantially collinearly arranged, with the chamber axes along its length.

13. The apparatus of any one of claims 2 to 12 wherein the minimum cross-sectional dimension of the outlet conduit is no smaller than the minimum cross-sectional dimension of the inlet conduit.

14. The apparatus of claim 13 when appended to claim 7 wherein the minimum cross-sectional dimension of the outlet conduit is no smaller than the minimum cross-sectional dimension of the transfer conduit, and the minimum cross-sectional dimension of the transfer conduit is no smaller than the minimum cross-sectional dimension of the inlet conduit.

15. The apparatus of any one of claims 2 to 14 wherein the mixing apparatus has a pair of inlets (13,15) in fluid communication with the inlet conduit, the inlets being arranged to introduce different fluids in side-by-side relation in the inlet conduit.

16. The apparatus of claim 15 wherein the inlet conduit has branch sections (19,21) connected to the inlets.

17. The apparatus of any one of the preceding claims sized for use in a micromixing process.

18. The apparatus of claim 17 comprised in a lab-on-a-chip device (51).

19. The apparatus of any one of the preceding claims formed in a unitary body (53).

20. The apparatus of claim 19 wherein the first vortex chamber is formed as a recess in a first side (55) of the body and the second vortex chamber is formed as a recess in a second side (57) of the body.

21. The apparatus of claim 20 when appended to claim 2 wherein the inlet conduit takes the form of a groove in the first side and the outlet conduit either takes the form of a groove in the second side or extends from the second vortex chamber, in the second side, to the first side.

22. The apparatus of claim 20 or 21 wherein the body is covered on the first and second sides by a cover layer (59,61) to enclose the vortex chambers.

23. A method of mixing a plurality of fluids in which the fluids are rotated together in a first vortex chamber (7) in a first rotating sense (X) and subsequently rotated in a second vortex chamber (27) in a second rotating sense (Y) which is opposite to that of the first rotating sense.

24. The method of claim 23 in which the contra-rotating steps are successive steps.

25. The method of claim 23 or 24 in which the fluids are introduced into the first vortex chamber concurrently.

26. The method of claim 23, 24 or 25 in which the fluids are introduced into the first vortex chamber from a common inlet (23).

27. The method of claim 25 or 26 in which the fluids are introduced concurrently as parallel flow streams.

28. The method of any one of claims 23 to 27 in which the first and second vortex chambers are formed in a lab-on-a-chip device (51).

29. The method of any one of claims 23 to 28 which is a passive mixing method.

30. A mixing apparatus (1) for mixing fluids having:-

a first vortex mixer (3) with a first vortex chamber (7) having a chamber axis (A-A), and

a second vortex mixer (5) with a second vortex chamber (27) which has a chamber axis (A-A) and which is in fluid communication with, and located downstream from, the first vortex chamber,

wherein the vortex mixers are arranged in the apparatus so that the chamber axes are axially aligned with the first and second vortex chambers overlaying one another.

31. The apparatus of claim 30 having a body (53) with first and second opposed sides (55,57), the first and second vortex chambers being respectively formed in the first and second sides of the body.

32. The method of any one of claims 23 to 29 implemented on the mixing apparatus of any one of claims 1 to 22, 30 and 31.

33. A mixing apparatus for mixing fluids substantially as hereinbefore described with reference to, and as illustrated by, the accompanying FIGURES of drawings.

34. A method of mixing a plurality of fluids substantially as hereinbefore described with reference to, and as illustrated by, the accompanying FIGURES of drawings.

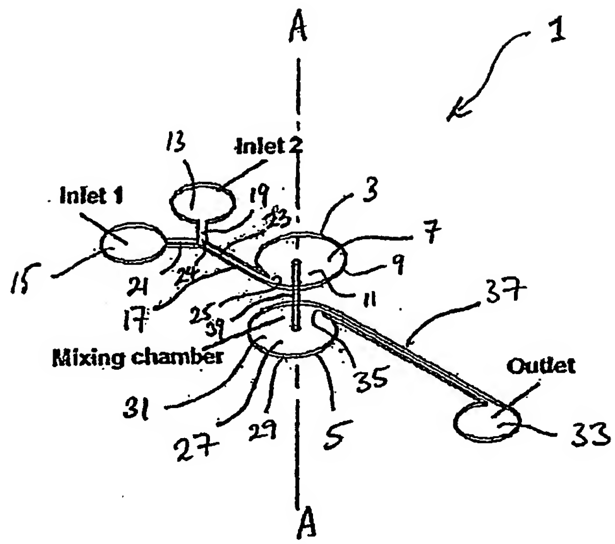

A
1
13
Inlet 2
Inlet 1
19
3
7
9
15
21
24
11
37
17
25
39
Mixing chamber
Outlet
35
31
27
29
5
33
A

FIG. 1

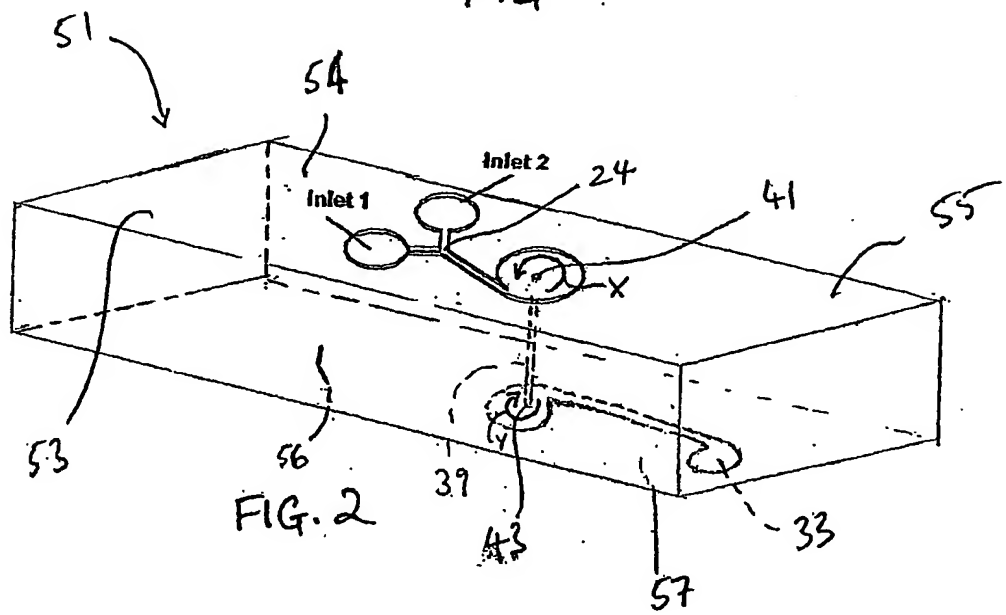

51
54
Inlet 2
24
Inlet 1
41
55
X
53
56
39
43
33
57

FIG. 2

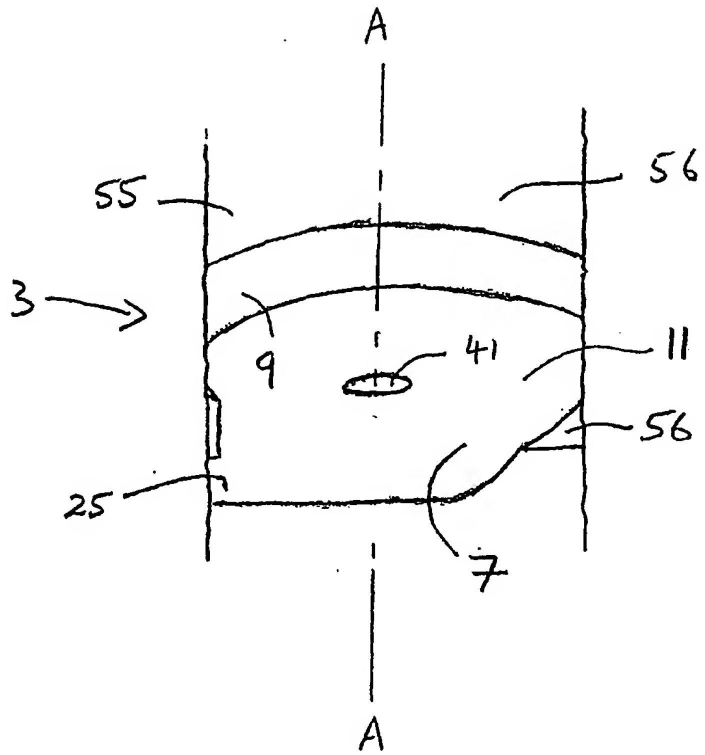


FIG. 3A

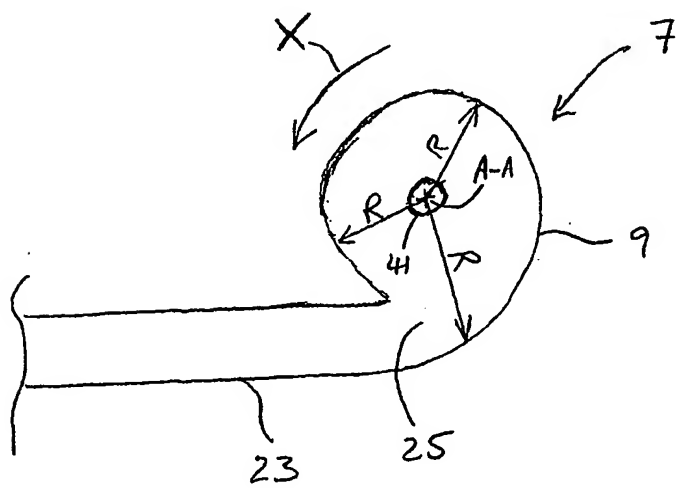


FIG. 3B

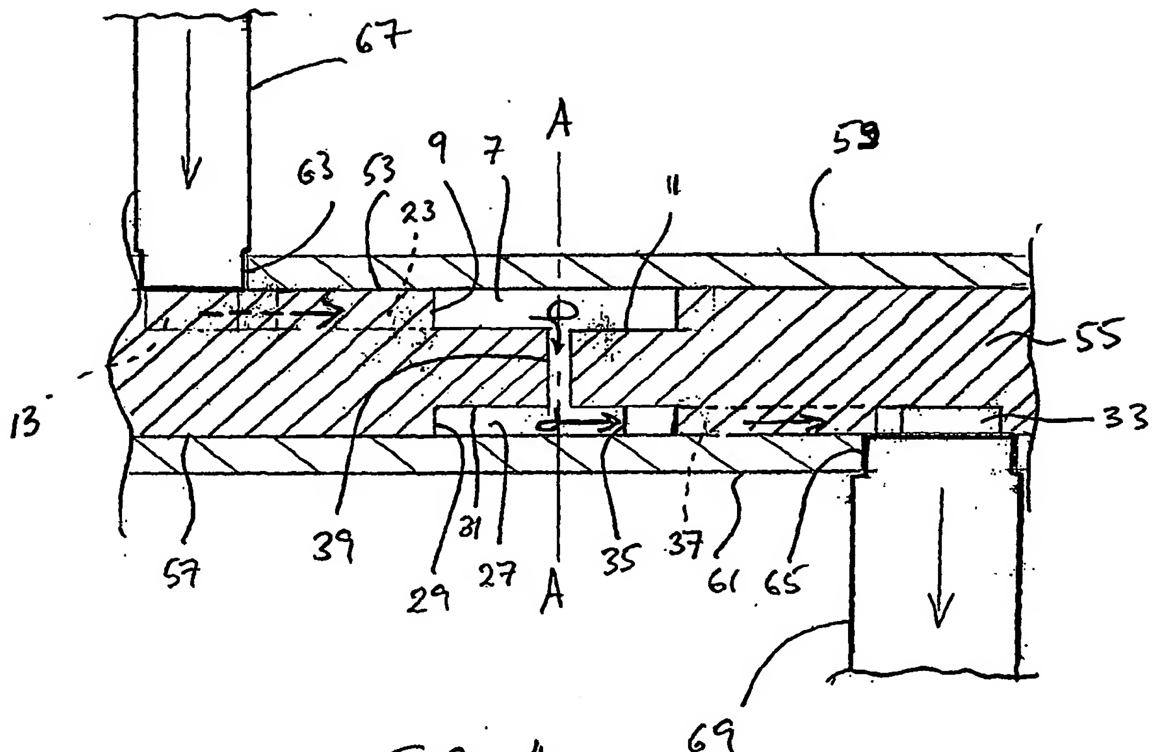


FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14509

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01F5/00 B01L9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01F B01J B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 415 275 A (DIETRICH DAVID E) 15 November 1983 (1983-11-15) the whole document	1,23-27, 29-34
X	DE 196 15 065 A (KASANMASCHEFF WALTER) 23 October 1997 (1997-10-23) column 2, line 60 - column 3, line 27; figure 1	1,23-26, 29,32,34
A	US 2001/048900 A1 (KLEIN GERALD L ET AL) 6 December 2001 (2001-12-06) the whole document	1-34
A	DE 532 532 C (PAUL LECHLER FA) 31 August 1931 (1931-08-31) the whole document	1-34

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2004	31/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/33585 A (CALIFORNIA INST OF TECHN) 6 August 1998 (1998-08-06) the whole document	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/14509

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4415275 A	15-11-1983	US 4480925 A	06-11-1984
DE 19615065 A	23-10-1997	DE 19615065 A1	23-10-1997
US 2001048900 A1	06-12-2001	CA 2408353 A1	29-11-2001
		CA 2408574 A1	29-11-2001
		EP 1289658 A2	12-03-2003
		EP 1286913 A2	05-03-2003
		JP 2003534504 T	18-11-2003
		JP 2004502926 T	29-01-2004
		WO 0189695 A2	29-11-2001
		WO 0189696 A2	29-11-2001
		WO 0189675 A2	29-11-2001
		WO 0190614 A2	29-11-2001
		WO 0189691 A2	29-11-2001
		WO 0189682 A2	29-11-2001
		WO 0189692 A2	29-11-2001
		US 6431212 B1	13-08-2002
		US 2001042712 A1	22-11-2001
		US 2002003001 A1	10-01-2002
		US 2002025279 A1	28-02-2002
		US 2001048637 A1	06-12-2001
		US 2002119078 A1	29-08-2002
		US 2001046701 A1	29-11-2001
DE 532532 C	31-08-1931	NONE	
WO 9833585 A	06-08-1998	AU 6152498 A	25-08-1998
		EP 1030733 A1	30-08-2000
		US 5921678 A	13-07-1999
		WO 9833585 A1	06-08-1998